

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/01890 A1

- (51) International Patent Classification⁷: A61F 2/06, A61P 35/00, A61K 9/00
- (21) International Application Number: PCT/US00/40105
- (22) International Filing Date: 6 June 2000 (06.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/346,975 2 July 1999 (02.07.1999) US
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- (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK,
DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/01890 A1

(54) Title: STENT COATING

(57) Abstract: A stent having a polymeric coating for controllably releasing an included active agent. The polymeric coating includes a blend of a first polymeric material, which if alone, would release the agent at a first, higher rate, and a second polymeric material, which if alone would release the agent at a second, lower rate over a longer time period. One stent coating utilizes a faster releasing hydrophilic polymeric material and a slower releasing hydrophobic material. One stent coating includes a blend of a faster releasing PLA-PEO copolymer and a slower releasing PLA-PCL copolymer. One active agent is Taxol. One use of the Taxol delivering stent is to inhibit restenosis following angioplasty.

STENT COATING

Field of the Invention

The present application is generally related to medical devices. More specifically, the present invention relates to stent coatings capable of releasing agents
5 over time. In particular, the present invention includes a blend of two co-polymers adapted to release restenosis-inhibiting agents over a sustained time period.

Background of the Invention

Vascular disease is a leading cause of death and disability in the developed world. In the United States, more than half of all deaths are due to cardiovascular
10 disease. Atherosclerosis is the most common form of vascular disease and leads to insufficient blood supply to body organs, which can result in hearts attacks, strokes, and kidney failure. Atherosclerosis is a form of vascular injury in which the vascular smooth muscle cells in the artery wall undergo hyperproliferation and invade and spread into the inner vessel lining, which can make the vessels susceptible to
15 complete blockage when local blood clotting occurs. This can lead to death of the tissue served by that artery. In the case of a coronary artery, this blockage can lead to myocardial infarction and death.

Coronary artery blockage can be treated with coronary artery bypass surgery and/or angioplasty. Both procedures may initially appear to be successful, but can be
20 in effect undone by the effect of restenosis, or the recurrence of stenosis after such a treatment. Restenosis is believed to include hyperproliferation of vascular smooth muscle cells. In particular, about one third of patients treated using angioplasty have restenosis and blockage within 6 months after the procedure.

To prevent vessel blockage from restenosis, stents are used. Stents are
25 nominally tubular structures and can have either solid walls or lattice like walls, and

can be either balloon expandable or self-expanding. After angioplasty balloon dilatation, the previously constricted vessel is at least temporarily widened. A stent can be delivered on a catheter and expanded in place or allowed to expand in place against the vessel walls. With the stent in place, restenosis may or may not be inhibited, but the probability and/or degree of blockage is reduced due to the structural strength of the stent opposing the inward force of any restenosis. Restenosis may occur over the length of the stent and be at least partially opposed by the stent. Restenosis may also occur past the ends of the stent, where the inward forces of the stenosis are unopposed.

10 Therapeutic agents to inhibit restenosis have been used with varying success. Taxol, an antimicrotubule agent isolated from the bark of the western Pacific Yew tree, is especially effective in inhibiting some cancers and is believed to be effective in combating restenosis. Systemic administration of Taxol can have undesirable side effects, making local administration a preferred mode of treatment.

15 Local administration of Taxol may be more effective when carried out over a longer time period, such as a time period at least matching the normal reaction time of the body to the angioplasty. At the same time, it may be desirable to provide an initial high dosage of Taxol over an initial period. Local administration of Taxol over a period of days or even months may be most effective in inhibiting restenosis.

20 Controlled release of therapeutic agents can utilize various technologies. Devices are known having a monolithic layer or coating incorporating a heterogeneous solution and/or dispersion of an active agent in a polymeric substance, where the diffusion of the agent is rate limiting, as the agent diffuses through the polymer to the polymer-fluid interface and is released into the surrounding fluid. In
25 some devices, a soluble substance is also dissolved or dispersed in the polymeric

material, such that additional pores or channels are left after the material dissolves. A matrix device is generally diffusion limited as well, but with the channels or other internal geometry of the device also playing a role in releasing the agent to the fluid. The channels can be pre-existing channels or channels left behind by released agent or
5 other soluble substances.

Erodible or degradable devices typically have the active agent physically immobilized in the polymer. The active agent can be dissolved and/or dispersed throughout the polymeric material. The polymeric material is often hydrolytically degraded over time through hydrolysis of labile bonds, allowing the polymer to erode
10 into the fluid, releasing the active agent into the fluid. Hydrophilic polymers have a generally faster rate of erosion relative to hydrophobic polymers. Hydrophobic polymers are believed to have almost purely surface diffusion of active agent, having erosion from the surface inwards. Hydrophilic polymers are believed to allow water to penetrate the surface of the polymer, allowing hydrolysis of labile bonds beneath
15 the surface, which can lead to homogeneous or bulk erosion of polymer.

What would be desirable is a stent coating capable of releasing a therapeutic agent over a sustained time period. What would be advantageous is a stent coating able to release an agent over approximately the same time period as the need for the therapeutic agent. A method for controlling the dosage rate and period of an active
20 agent by controlling the composition of a stent coating would also be advantageous.

Summary of the Invention

The present invention includes a stent having a stent body, a coating disposed over at least a portion of the body, and an active agent releasably dispersed in at least part or portion of the coating. A preferred active agent is paclitaxel, analogues, derivatives,
25 and combinations thereof. The coating can include a blend of a first co-polymer

having a first, high release rate and a second co-polymer having a second, lower release rate relative to the first release rate. The first and second copolymers are preferably erodible or biodegradable. In one embodiment, the first copolymer is more hydrophilic than the second copolymer. In one embodiment, the first copolymer includes a polylactic acid/polyethylene oxide (PLA-PEO) copolymer and the second copolymer includes a polylactic acid/polycaprolactone (PLA-PCL) copolymer.

The relative amounts and dosage rates of active agent delivered over time can be controlled by controlling the relative amounts of the faster releasing polymers relative to the slower releasing polymers. For higher initial release rates the proportion of faster releasing polymer can be increased relative to the slower releasing polymer. If most of the dosage is desired to be released over a long time period, most of the polymer can be the slower releasing polymer. The stent can be coated by spraying the stent with a solution or dispersion of polymer, active agent, and solvent. The solvent can be evaporated, leaving a coating of polymer and active agent. The active agent can be dissolved and/or dispersed in the polymer. In some embodiments, the co-polymers can be extruded over the stent body.

In use, the stent can be put into position in a body vessel such as a coronary vessel after a procedure such as angioplasty. The stent can be left in position, and the erodible or biodegradable coating allowed to degrade. As the polymeric coating degrades, the active agent can absorb into the vessel walls.

Description of the Drawings

Fig. 1 is a perspective view of a stent in accordance with an exemplary embodiment of the present invention;

Fig. 2 is a perspective view of a further preferred stent in accordance with the present invention; and

Fig. 3 is a magnified, partial plan view of the stent of Fig. 1, illustrating the polymeric coating of the present invention disposed thereon.

Detailed Description of the Invention

The present invention includes a stent having a polymeric coating for
5 delivering a biologically active agent or other therapeutic substance over a target time period. The polymeric coat includes a first polymer and a second polymer, where the first polymer alone would release the active agent at a faster rate than the second polymer would alone, and thus, deplete the active agent immobilized by the first polymer in a shorter time relative to the second polymer. In preferred embodiments,
10 the first polymer is hydrophilic and the second polymer is hydrophobic.

Referring now to the drawings wherein like reference numerals refer to like elements throughout the several views, Fig. 1 shows a perspective view of a stent 10, in a non-expanded form, in accordance with the present invention. The skeletal frame of the stent 10 preferably includes wire-like members 12 forming a distinct, repetitive
15 serpentine pattern. This repetitive serpentine pattern consists of multiple U-shaped curves 14. The areas within the U-shaped curves 14 are open 16. With no recognizable beginning or end to this serpentine pattern, wire 12 forms expandable serpentine element 18. Serpentine elements 18 are arranged along the longitudinal axis of the stent 10 so that the U-shaped curves 14 of abutting serpentine elements 16
20 may be joined through an interconnecting element 20. Through the interconnecting elements 20, a continuous wire 12 framework is created between multiple serpentine elements 18 forming the stent 10.

Fig. 2 shows a perspective view of a further preferred stent 110 in accordance with the present invention. This stent 110, also has a continuous wire 112 framework.
25 This framework, however, is maintained by a repetitive rectangular-patterned element

114. The areas within the rectangular wire element 114 are open 116. The rectangular wire elements 114 are aligned lengthwise in the longitudinal axis of the stent 110. Adjacent rectangular wire elements 114 are offset half the lengthwise distance of a similar rectangular wire element 114. The end of the stent is formed by
5 the full completion of one rectangular wire element 114, and the subsequent open end of the adjacent rectangular wire element 122. Thus, the ends of the stent possess an alternating open-closed wire configuration.

These stents are exemplary of stents which may incorporate the present invention. These, and other suitable stents are disclosed in U.S. Patent Application
10 Serial No. 08/874,190, filed June 13, 1997, entitled "Polymeric Layered Stent", of which the disclosure is incorporated herein by reference.

The term "wire", as used in describing the frame material, should not be mistaken as being limited to metallic materials. In fact, the "wire" forming the stents
10 & 110 may consist of any biocompatible material possessing the structural and
15 mechanical attributes necessary for supporting a diseased vessel. Thus, both metallic and polymeric materials are suitable. Examples of preferred biocompatible metallic materials include stainless steel, tantalum, nitinol, and gold. Preferred polymeric materials may be selected from the list immediately below, which is not exhaustive:

poly(L-lactide) (PLLA), poly(D,L-lactide) (PLA), polyglycolide (PGA),
20 poly(L-lactide-co-D,L-lactide) (PLLA/PLA), poly(L-lactide-co-glycolide) (PLLA/PGA), poly(D, L-lactide-co-glycolide) (PLA/PGA), poly(glycolide-co-trimethylene carbonate) (PGA/PTMC), polyethylene oxide (PEO), polydioxanone (PDS), polycaprolactone (PCL), polyhydroxybutyrate (PHBT), poly(phosphazene), polyD,L-lactide-co-caprolactone) (PLA/PCL),
25 poly(glycolide-co-caprolactone) (PGA/PCL), polyanhydrides (PAN),

poly(ortho esters), poly(phosphate ester), poly(amino acid), poly(hydroxy butyrate), polyacrylate, polyacrylamid, poly(hydroxyethyl methacrylate), elastin polypeptide co-polymer, polyurethane, polysiloxane and their copolymers.

5 The skeletal framework of the stents may be formed through various methods as well. The framework may be welded, molded, or consist of filaments or fibers which are wound or braided together in order to form a continuous structure.

Often it is beneficial to both stent and treat the localized area of a diseased vessel. A therapeutic agent, therefore, can be incorporated into a polymer and applied
10 to the stent 10 as a polymeric surface treatment. The incorporation of a therapeutic agent into a surface treatment greatly enhances the scope of this medical device by transforming the stent into a drug-delivery system. Drugs and treatments which utilize anti-thrombogenic agents, anti-angiogenesis agents, anti-proliferative agents, growth factors, and radiochemicals may be readily deployed from within the matrix of
15 the polymeric surface treatment. Specific examples of preferred therapeutic agents include angiopeptin, colchicine, lovastatin, trapidil, ticlopidine, hirudin, Taxol, heparin, and growth factors VEGF, TGF-beta, IGF, PDGF, and FGF.

The application of such a surface treatment is generally accomplished through either a dipping or spraying process. For either process, a solvent carrier is preferred
20 in order to incorporate the therapeutic agent within the polymer matrix. The applied mixture preferably comprises a solvent, a polymer, and a therapeutic agent, with subsequent evaporation of the solvent to leave a polymeric coating 30 as depicted in Fig. 3.

As previously stated, the present invention is directed to a polymeric coating
25 incorporating a releasable therapeutic agent, wherein upon implantation the rate and

duration of the agent is controlled to selected parameters which optimize treatment. It has been found that selected ratios of a mixture of a hydrophilic polymer and a hydrophobic polymer provide desired control of drug release.

In a preferred embodiment, the hydrophilic polymer includes a co-polymer of poly(lactic acid) (PLA) and poly(ethylene oxide) (PEO). In a preferred embodiment, the second polymer includes a co-polymer of poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL). The PLA-PEO copolymer is hydrophilic and erodes faster relative to a similar hydrophobic polymer in the body environment where the coated stent is positioned. The PLA-PCL copolymer is hydrophobic, and degrades more slowly than a comparable hydrophilic polymer. In a preferred embodiment, the polymer coating is formed of a blend of PLA-PCL and PLA-PEO. In preferred embodiments, the hydrophilic polymer has a molecular weight of greater than about 10,000 (Mn) and the second polymer has a molecular weight of greater than about 20,000 (Mn).

Formation of PLA-PEO copolymers is well known to those skilled in the art. See for example, U.S. Patent Nos. 5,476,909 and 5,548,035, herein incorporated by reference. Formation of PLA-PCL copolymers is also known to those skilled in the art. See for example, U.S. Patent No. 5,470,829, herein incorporated by reference.

One preferred embodiment includes about 20% by weight PLA-PEO and about 80% by weight PLA-PCL copolymers. Another embodiment includes about 50% by weight PLA-PEO copolymer and about 50% by weight PLA-PCL copolymer. The embodiment having about 20% PLA-PEO and 80% PLA-PCL delivers the active agent over a longer time period, but with a lower initial release, relative to the embodiment having the 50%/50% PLA-PEO/PLA-PCL combination. The relative amounts of PLA-PEO and PLA-PCL can be adjusted to achieve the desired

combination of high initial dosage rate and subsequent lower but longer lasting dosage rate.

In one preferred embodiment, the active agent or therapeutic substance is a restenosis-inhibiting agent. A preferred restenosis-inhibiting agent includes a
5 microtubule stabilizing agent such as Taxol, paclitaxel, analogues, derivatives, and mixtures thereof. For example, derivatives believed suitable for use in the present invention include 2'-succinyl-taxol, 2'-succinyl-taxol triethanolamine, 2'-glutaryl-taxol, 2'-glutaryl-taxol triethanolamine salt, 2'-O-ester with N-(dimethylaminoethyl) glutamine, and 2'-O-ester with N-(dimethylaminoethyl) glutamide hydrochloride salt.

10 The Taxol can be dissolved or dispersed in the polymeric materials and the polymeric materials adhered to the stent body. In embodiments having a blended combination of PLA-PEO and PLA-PCL, the polymeric combination can be sprayed, dipped or extruded onto the stent.

The polymeric coating of the present invention can be used with various
15 stents. A preferred use for the coating is for coronary stents. The stents can be used following angioplasty to inhibit restenosis. The stent body can serve to hold the vessel open against any restenosis and to deliver the restenosis-inhibiting agent. In one embodiment, the coating is substantially continuous over the stent body. In another embodiment, the coating is primarily over the stent structure but not over the
20 apertures. For example, in a stent formed of a wire mesh, the coating can closely adhere to the wires without covering the apertures therebetween.

In use, a stent according to the present invention can be selected according to desired release dosage profile and provided to the treating physician. After an angioplasty procedure, the coated stent having the restenosis-inhibiting active agent
25 can be delivered to the stenosed, recently dilated coronary artery region. Delivery can

be accomplished using methods well known to those skilled in the art, such as mounting the stent on an inflatable balloon disposed at the distal end of a catheter. With the stent advanced into position near the dilated region, the stent can be forced outward and into position against the inner vessel walls. If the stent is self-expanding, the stent can be delivered by deploying the stent from within a delivery device, allowing the stent to expand against the inner vessel walls. The active agent, as it is released from the eroding polymeric coating, can be absorbed by the inner vessel walls. Over time, the polymeric coating is eroded by bodily fluids.

Numerous advantages of the invention covered by this document have been set forth in the foregoing description. It will be understood, however, that this disclosure is, in many respects, only illustrative. Changes may be made in details, particularly in matters of shape, size, and arrangement of parts, without exceeding the scope of the invention. The inventions's scope is, of course, defined in the language in which the appended claims are expressed.

What is claimed is:

1. A stent comprising:
a stent body;
a coating disposed over at least a portion of said body; and
a biologically active agent dispersed in said coating, wherein said coating includes a mixture of a first co-polymer and a second co-polymer, wherein said first co-polymer releases said agent at a first rate and said second co-polymer release said agent at a second rate, wherein said second rate is slower than said first rate, such that said agent is released from said coating at a rate slower than said first rate and faster than said second rate.
2. A stent as recited in claim 1, wherein said first co-polymer is hydrophilic.
3. A stent as recited in claim 1, wherein said second co-polymer is hydrophobic.
4. A stent as recited in claim 1, wherein said first co-polymer is hydrophilic and said second co-polymer is hydrophobic.
5. A stent as recited in claim 1, wherein said first co-polymer includes PLA-PEO.
6. A stent as recited in claim 1, where said second co-polymer includes PLA-PCL.

7. A stent as recited in claim 1, wherein said first co-polymer includes PLA-PEO and said second co-polymer includes PLA-PCL.

8. A stent as recited in claim 7, wherein said agent includes an agent selected from the group consisting of paclitaxel, paclitaxel analogues, paclitaxel derivatives, and combinations thereof.

9. A stent for controllably releasing a biologically active agent over a long time period comprising:

a stent body;

a biologically active agent; and

means for adhering said agent to said stent body and controllably releasing said agent from said stent body over time, wherein said means for controllably releasing said agent includes a combination of a first means for releasing said agent at a first rate over a first time period and second means for releasing said agent at a second rate over a second time period, wherein said first rate is faster than said second rate and said first period is shorter than said second period.

10. A stent as recited in claim 9, wherein said first means for releasing includes a bioabsorbable polymeric material and second means for releasing includes a bioabsorbable polymeric material, wherein said first means is absorbed faster than said second means.

11. A stent for releasing a biologically active agent inside the human body comprising:

a stent body;

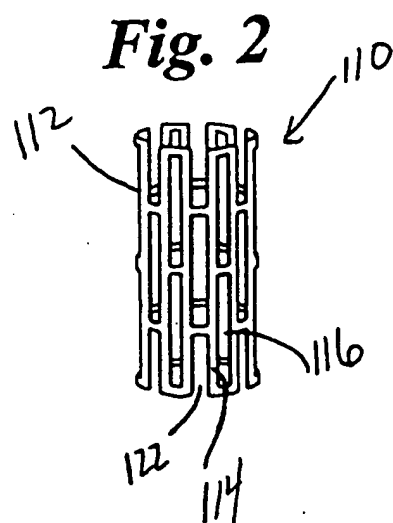
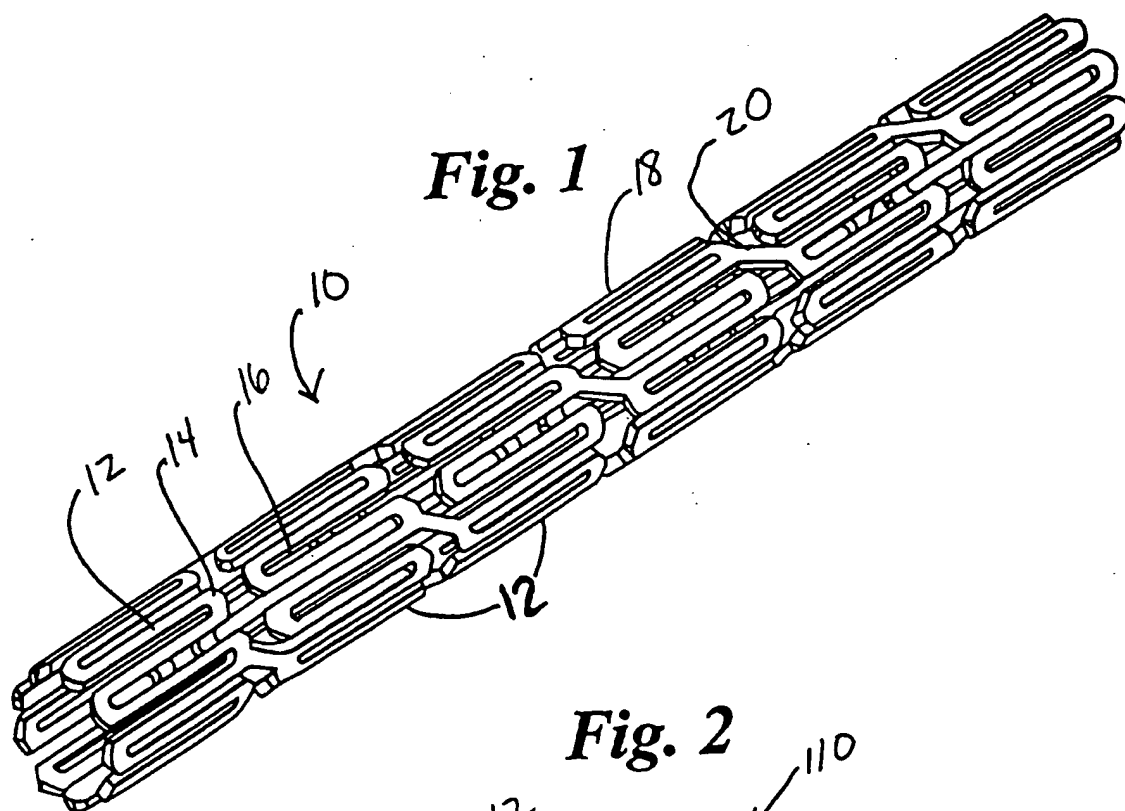
a polymeric coating disposed over at least a part of said stent body; and

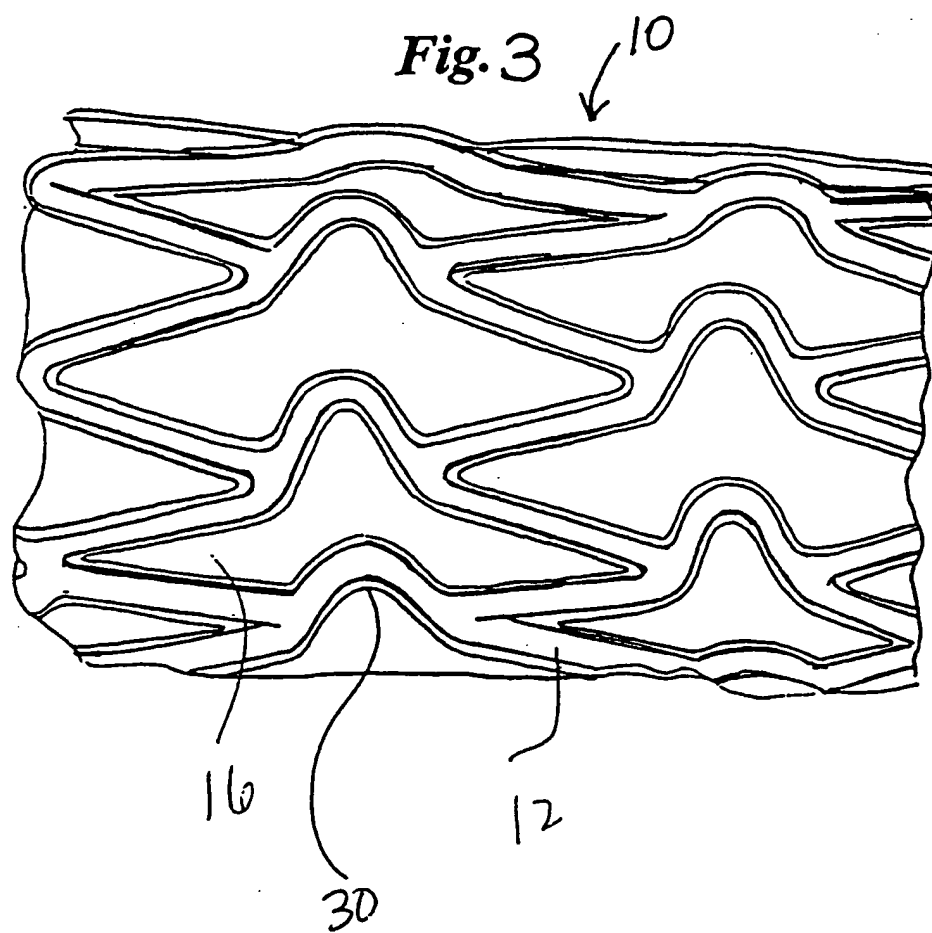
a biologically active material admixed with said polymeric coating, wherein said polymeric coating includes a blend of a PLA-PEO copolymer and a PLA-PCL copolymer.

12. A stent as recited in claim 11, wherein said biologically active agent includes an agent selected from the group consisting of paclitaxel, paclitaxel analogues, paclitaxel derivatives, and combinations thereof.

13. A method for inhibiting restenosis comprising the steps of:

providing a stent including a coating having a blend of a PLA-PEO copolymer and a PLA-PCL copolymer, wherein said coating includes a restenosis inhibiting agent selected from the group consisting of paclitaxel, paclitaxel analogues, paclitaxel derivatives, and combinations thereof mixed therein, such that said agent is released over a time period longer than would be released by said PLA-PEO copolymer alone, and released over a time period shorter than would be released PLA-PCL copolymer alone.





INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/40105

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61F2/06 A61P35/00 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | WO 98 56312 A (SCIMED LIFE SYSTEMS, INC.) 17 December 1998 (1998-12-17) cited in the application the whole document | 1-13 |
| Y | WO 99 21908 A (ANGIOTECH PHARMACEUTICALS, INC. ET AL.) 6 May 1999 (1999-05-06) page 2, line 23 -page 3, line 11 page 14, line 18 -page 20, line 5 page 50 -page 53; example 5 page 69 -page 70; example 13 | 1-13 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

12 December 2000

Date of mailing of the international search report

19/12/2000

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/40105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | E.M. JARR ET AL.: "Sustained release of lidocaine from an injectable implant system for treatment of post-operative pain" PROCEED. INT. SYMP. CONTROL. REL. BIOACT. MATER., vol. 26, July 1999 (1999-07), pages 631-632, XP002133945 the whole document | 1-13 |
| Y | EP 0 737 703 A (POLY-MED INC.) 16 October 1996 (1996-10-16) page 13; example 4 | 1-13 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: International Application No

PCT/US 00/40105

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---------------------|----------------------------|-----------|---------------------|
| WO 9856312 | A | 17-12-1998 | NONE | | |
| WO 9921908 | A | 06-05-1999 | AU | 9617698 A | 17-05-1999 |
| EP 737703 | A | 16-10-1996 | US | 5612052 A | 18-03-1997 |
| | | | AU | 685357 B | 15-01-1998 |
| | | | AU | 5056196 A | 31-10-1996 |
| | | | CA | 2174072 A | 14-10-1996 |
| | | | DE | 737703 T | 15-05-1997 |
| | | | JP | 9100343 A | 15-04-1997 |
| | | | US | 5714159 A | 03-02-1998 |